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EXAMINER

PORTNER, VIRGINIA ALLEN

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 11/15/2002

W

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/884,696

Applicant(s)
George et al

Examiner
Partner

Art Unit
1645



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Aug 27, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 12-15, and 23-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claims 1-33 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 6/19/01 is/are a) ☐ accepted or b) ☒ objected to by the Examiner. *Figure 7 should be 7A+7B*
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7 6) ☐ Other:

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DETAILED ACTION

Claims 1-33 are pending.

Election/Restriction

1. Claims 8-11, 16-22 and 26-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups II-XI, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9, dated August 19, 2002.
2. Applicant's election with traverse of Group I, Claims 1-7, 12-15, 23-25, drawn to a peptides, polypeptides, or a cytotoxin protein defined by SEQ ID Nos 1 or 2, and specific peptides encoded by SEQ ID No 6 or 13, classified in class 530, subclass 350, in Paper No. 9, is acknowledged.
3. The traversal is on the ground(s) that "on the basis that at least with regard to Group I and III, the restriction is not proper", and states "Once Examiner searches the Group I for references to cytotoxin of *M. bovis*, any method for diagnosis or prophylaxis will necessarily be found and by the same correlation, when Group III or IV would be searched, *M. bovis* cytotoxin reference would be found. The claims of Groups I, III and IV are related as a composition and the use for such composition." The claims in Groups I, III and IV are asserted to not constitute a serious burden and are respectively requested to be examined at the same time. These arguments have been fully considered but are not found to be persuasive for the reasons below.

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

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The term “distinct” is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.1). In the instant situation, the inventions of Groups 1, III, and IV, as well as Groups II, V-XI are drawn to distinct inventions which are related as separate products capable of separate functions. Restrictions between the inventions is deemed to be proper for the reason previously set forth.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. In the instant case a burden has been established in showing that the inventions of Groups I-XI are classified separately necessitating different searches of issued US Patents. However, classification of subject matter is merely one indication of the burdensome nature of search. The literature search, particularly relevant in this art, is not co-extensive, because for example genes, proteins, diagnostic fragments, and antigens would differ from method of using these products as the combination of reagents would differ. Additionally, it is submitted that the inventions of Groups I-XI have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made Final.

Please Note: The examiner is reading all of the claims as product by process claims, and the Moraxella bovis cytotoxin of claim 1 is not limited to a cytotoxin encoded by SEQ ID NO 1. Claim 1 claims a product, which can be produced by the recited process step of “produced” and the claimed product produced by a materially different process would anticipate the claimed invention.

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Claim Rejections - 35 U.S.C. § 101

4. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 12-14 are directed to an amino acid sequence that is not isolated and purified; the claims do not show the "hand of man." The claimed invention is directed to non-statutory subject matter.

Claim Rejections - 35 U.S.C. § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of recombinant *Moraxella bovis* cytotoxin comprising SEQ ID NO 2, and fragments of SEQ ID NO 2, does not reasonably provide enablement for the utilization of any fragments of SEQ ID No 2, to include SEQ ID NO 6 or 13 as vaccines. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification fails to teach how to formulate and use the claimed vaccines that comprises any fragment of SEQ ID NO 2. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to treat or prevent infection or disease induction. The specification teaches a *Moraxella bovis* cytotoxin of SEQ ID NO 2 that is able to induce a protective immune response when combined with an adjuvant.

The specification does not provide substantive evidence that the claimed vaccines that comprises any cytotoxin fragment or a composition with out an adjuvant are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing *Moraxella bovis* infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the at protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro

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neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

9. Claims 12-15 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claimed invention is directed to recombinant proteins (claim 15, 23-25) that comprise an amino acid sequence fragment of SEQ ID NO 2, or is encoded by gene that comprises a fragment of SEQ ID NO 1 (nucleic acid), an amino acid sequence that comprises fragment of SEQ ID No. 2 (claims 12-14), or a recombinant protein that comprises an amino acid sequence of SEQ ID NO 2, 6 or 13. What all of the DNA sequences that comprise a fragment of SEQ ID NO 1, and comprise an amino acid fragment of SEQ ID NO 2, as well as what all the proteins are that

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comprise any fragment of SEQ ID NO 2, 6 or 13 from any source, and would serve as a recombinant vaccine have not been described.

The specification discloses recombinant proteins which may evidence alterations in the amino acid sequence, and which would evidence changes in the nucleic acid molecule but what alterations are in the claimed plurality of recombinant proteins, encoded by the recombinant genes that encode the plurality of proteins, that are not a *Moraxella bovis* cytotoxin, of SEQ ID NO 2, encoded by SEQ ID No 1, or is a fragment of SEQ ID NO 6 or 13, have not been described.

A description of a genus may be achieved by means of a recitation of a representative species, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398-1412, 1406 (Fed. Cir. 1997).

The claimed amino acid sequences (claims 12-14), recombinant protein (claim 15), or recombinant cytotoxin that comprises an amino acid sequence fragment of SEQ ID No 2, or is encoded by a DNA that comprises a fragment of SEQ ID NO 1, the products of which do not have any specific function but must only share a common amino acid sequence, have not been described.

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus recombinant proteins (claim 15)

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that have alterations in their gene loci (nucleic acid molecules that encode a plurality of proteins). Even if the claims were amended to require the encoded recombinant protein to evidence cytotoxic activity, only 4 species of the now claimed genus have been described and shown in figure 4-1.

There is no description of where or how the alterations must be made in the gene loci to achieve or maintain a hemolytic, leukotoxic or corneotoxic effect, or for the induction of a protective immune response upon administration of the recombinant protein to a host to protect against *Moraxella bovis* challenge, using any recombinant protein, that only shares a fragment of SEQ ID No 2, and is encoded by a gene that comprises only a fragment of SEQ ID No 1.

The specification proposes to discover other members of the genus by using sequence homologies and introduction of alterations based upon what is already known. Altered genes that have structural features that could distinguish the claimed amino acid sequence and recombinant proteins from others excluded are missing from the disclosure.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

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Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlag, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Amino acid sequences that comprise a fragment of SEQ ID NO 2 (claims 12-14), recombinant proteins that comprise a fragment of SEQ ID NO 1 (claims 15 and 23-25), a recombinant protein homolog or allelic variant that shares a fragment sequence with SEQ ID No 2 and is able to induce a protective immune response against *Moraxella bovis* (claims 23-25) have not been described. Sufficient support for the generic claims has not been provided.

See the Interim Guidelines on Written Description, (Fed Reg , June 15, 1998, Volume 63, Number 114, pages 32639-32645) and the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

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10. Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the phrase “a cytotoxin-enriched fraction”. Claim 5 broadens the scope of claims 1-4 from which claim 5 depends, in light of the fact that claims 1-4 are directed to a purified or partially purified cytotoxin, and not an “enriched fraction” that comprises a plurality of cytotoxins. The word “fraction” lacks antecedent basis in claims 1-4. No column fractions were combined and diafiltrated. What is contained in the cytotoxin-enriched fraction? How does the enriched fraction of claim 5 further limit the purified cytotoxin of claims 1-4? An enriched fraction would be less pure than a purified composition; claim 5 does not further limit the purified compositions of claims 1-4.

Claim 6 is directed to a “hemolysin, leukotoxin or corneotoxin” and depends from claim 5. Claims 5 and 6 broaden the scope of claims 1-4 as three different types of cytotoxins are recited in claims 5-6. See Ruth Marrion, abstract page 4031-B that teaches *Moraxella* produces three different virulence factors, specifically a hemolysin, a cytotoxin and a leukotoxin.

Claim 7 defines the claimed cytotoxin to have a molecular weight of “about 95 and 98 kDa”. How can the cytotoxin have two different molecular weights simultaneously? Are two different molecules being claimed in claim 7, while claims 1-4 are directed to a single cytotoxin? Claim 7 is broader in scope than claims 1-4 from which it indirectly depends.

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Claim Rejections - 35 U.S.C. § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Case Law applicable to rejections set forth below: Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

12. Claims 1-7, 12-15 and 23-25 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 01/16172 A1, publication date 08 March 2001.

WO 01/16172 A1 discloses the claimed invention directed to a purified, partially purified or recombinantly produced *Moraxella bovis* cytotoxin, wherein the cytotoxin comprises the amino acid sequences of SEQ ID NO 6, SEQ ID No 13, and is purified from culture supernatants, purified by centrifugation, and has biological activity of a hemolysin, leukotoxin or corneotoxin with a relative molecular weight of about 95 to 98 kDa (see Figure 6, page 5, lines 25-33; page 7, lines 29-36; pages 11-13, 25-28) and sequence alignments attached hereto. WO 01/16172 A1 anticipates the instantly claimed invention.

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13. Claims 1-6, 12-15, 23 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 90/07525, publication date 12 July 1990. (Please Note: the phrase "a recombinant" is being read as a process step that produces a product equivalent to the naturally occurring purified cytotoxin).

WO 90/07525 discloses the claimed invention directed to a purified, or partially purified *Moraxella bovis* cytotoxin, wherein the cytotoxin, was isolated from *Moraxella bovis* strain Tifton 1 (see page 10, lines 8-10), the same strain from which the coding sequences SEQ ID NO 1 was determined for the instantly claimed invention.

The cytotoxin/hemolysin was purified from *Moraxella bovis* cultures that were harvested, centrifuged and filtered (see page 12, lines 3-30, especially paragraph 3.) or purified through a series of steps that would result in a cytotoxin equivalent to that which is present in a diafiltrate (see pages 4-5, starting at page 4, line 19 through page 5, line 31; page 17, section D., lines 25-35 and page 18). The purified cytotoxin evidenced leukotoxin activity (see pages 13-16, fractions 4, 20-21), and hemolytic activity (fractions 13-17, page 16), with a relative molecular weight of 42 kDa (see page 7, paragraph 2) . WO 90/07525 anticipates the instantly claimed invention.

14. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Billson et al,(1994 reference provided in Applicant's US-PTO 1449)

Billson et al discloses the claimed invention directed to a purified, or partially purified produced *Moraxella bovis* cytotoxin (see title and page 72, Table 2), wherein the cytotoxin was

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purified from culture supernatants, purified by centrifugation (see page 70, col. 1, paragraph 4, bottom of page), and diafiltration (ultrafiltration), and has biological activity of a hemolysin, leukotoxin or corneotoxin with a relative molecular weight of about 65 to 97 kDa (see page 73, col. 1, paragraphs 1-2). The reference by all comparable data, inherently, anticipates the instantly claimed invention.

15. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Billson et al, (June 2000, reference provided in Applicant's US-PTO 1449)

Billson et al discloses the claimed invention directed to a purified, or partially purified produced *Moraxella bovis* cytotoxin (see title and page 3469, materials and methods, paragraph 1), wherein the cytotoxin was purified from culture supernatants, purified by centrifugation (see page paragraph bridging pages 3469-3470), and diafiltration (ultrafiltration), and has biological activity of a hemolysin, leukotoxin or corneotoxin with a relative molecular weight of about 65 to 97 kDa (see page Figures 2-3, page 3471 and page 3472, Figures 4-5). The reference by all comparable data, inherently, anticipates the instantly claimed invention.

16. Claims 12-15 and 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by CA2014033-A (publication date October 7, 1990; *Pasterurella haemolytica* leukotoxin).

CA2014033-A disclose the claimed invention directed to an amino acid sequence (claims 12-14), recombinant protein (claim 15), and a composition that comprises a recombinant

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cytotoxin (claim 23-25) that comprises “an amino acid sequence depicted by SEQ ID NO 2 or a fragment thereof (see sequence alignment with SEQ ID NO 1(which encodes SEQ ID No 2), 6 and 13 . The reference anticipates the instantly claimed invention.

17. Claims 12, 14-15 and 23, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat. 5,475,098 (see sequence alignment for SEQ ID NO 13, E. Coli).

US Pat. 5,475,098 discloses the claimed invention directed to an amino acid sequence (claims 12, 14), recombinant protein (claim 15), and a composition that comprises a recombinant cytotoxin (claim 23,25) that comprises “an amino acid sequence depicted by SEQ ID NO 2 or a fragment thereof wherein the fragment is SEQ ID No. 13 . The reference anticipates the instantly claimed invention.

18. Claims 12, 14-15 and 23, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by CA2170839 (see sequence alignment for SEQ ID NO 13, Actinobacillus pleuropneumonia).

CA2170839 discloses the claimed invention directed to an amino acid sequence (claims 12, 14), recombinant protein (claim 15), and a composition that comprises a recombinant cytotoxin (claim 23,25) that comprises “an amino acid sequence depicted by SEQ ID NO 2 or a fragment thereof wherein the fragment is SEQ ID No. 13 . The reference anticipates the instantly claimed invention.

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Conclusion

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
20. Highlander et al (1989, sequence alignment for SEQ Id No 2) is cited to show leukotoxin A of *Pasteurella haemolytica* serotype 1 that shares 464 amino acids of instantly claimed SEQ ID No 2.
21. Halenda, Ruth Marrion (1998) is cited to show a composition of *Moraxella bovis* cytotoxin (see abstract of dissertation).
22. Ostle, AG et al (1985) is cited to the purification of hemolysin from *Moraxella bovis* and immunoreactivity of antibodies generated thereto with *M.bovis* strain Epp63 (see Table 3, page 1013)
23. Ostle, AG et al (1984) is cited to show *Moraxella bovis* hemolysin purified from broth culture supernatants (see Figure 1, Table 2, page 1849; Table 3, page 1850).
24. Sandhu et al (1977) is cited to show production and characterization of *Moraxella bovis* hemolysin (see Figures 1 and 2, page 884).
25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

November 12, 2002


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